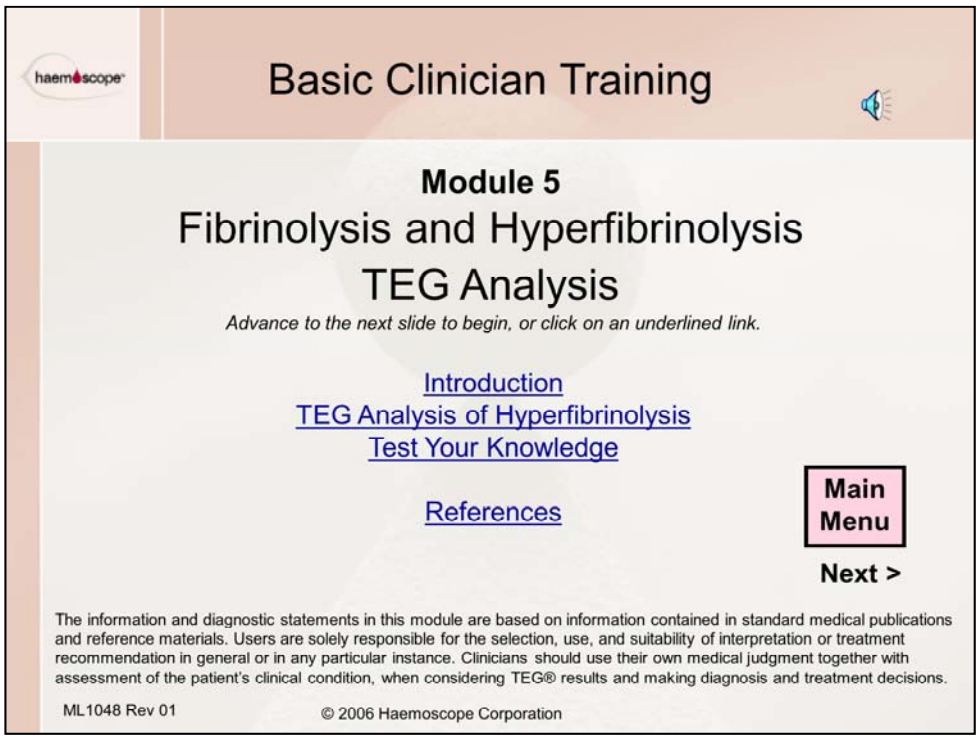
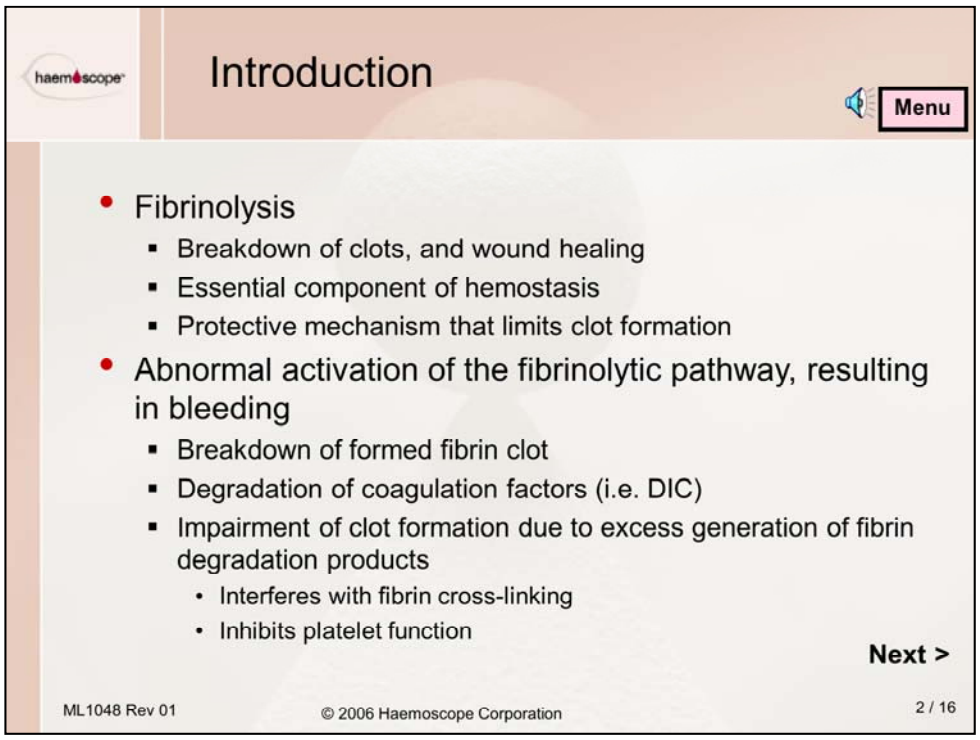


This module discusses fibrinolytic and hyperfibrinolytic states, and how the TEG analyzer can be used to determine the extent and cause of fibrinolysis.

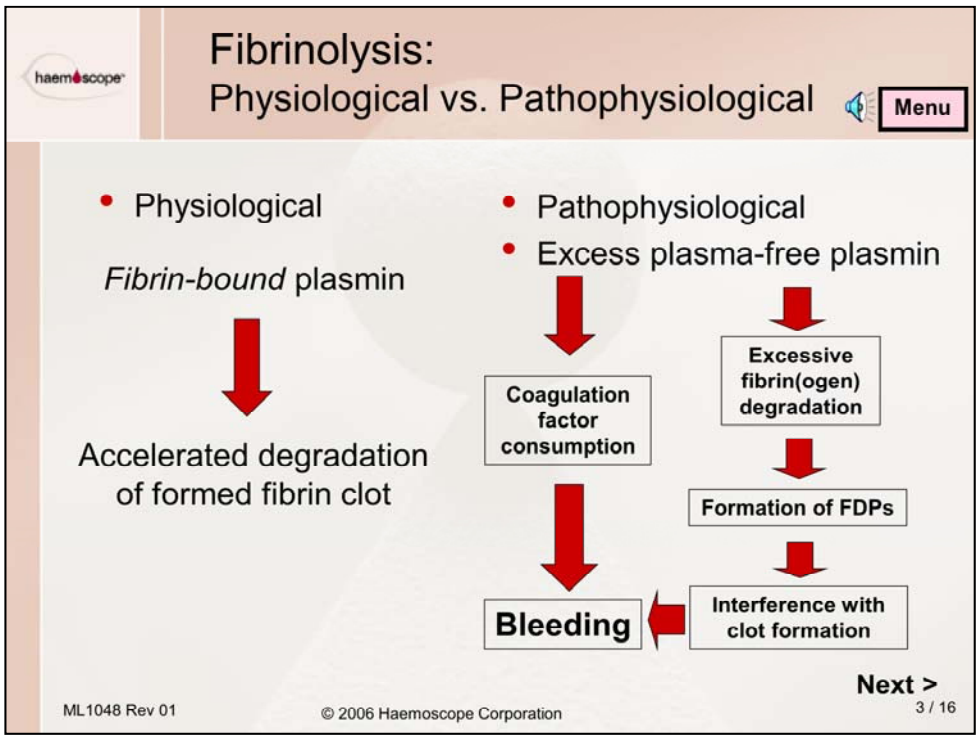
Advance to the next slide to begin the presentation, or click on an underlined link to proceed to a specific topic.



Fibrinolysis is associated with the breakdown of clots and with wound healing. It is an essential component of the hemostatic system, and is a protective mechanism that limits the extent of clot formation, helping to maintain blood flow by keeping the vasculature clear of thrombi.

However, abnormal activation of the fibrinolytic pathway can result in bleeding. Along with the breakdown of clots prior to completion of wound healing, excessive fibrinolysis breaks down coagulation factors in addition to fibrin, impairing the ability to form clots. Bleeding can also occur when the rate of fibrinolysis is greater than the rate of clot development, resulting in reduced clot formation.

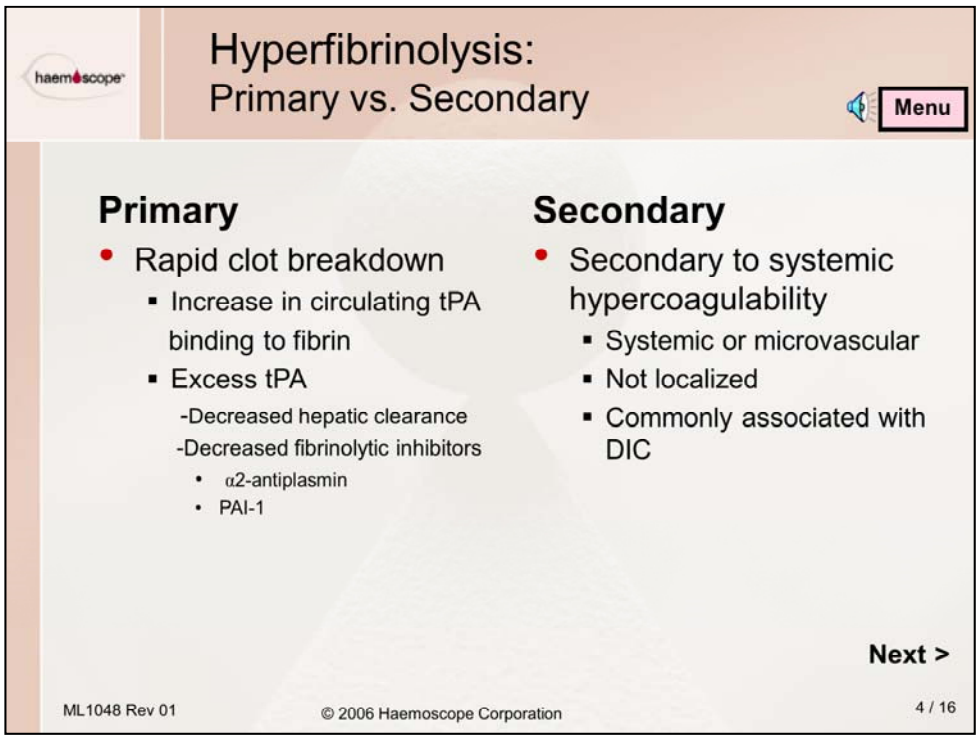
Finally, excessive fibrinolysis impairs clot formation by generating fibrin degradation products (FDPs). These interfere with fibrin cross-linking and inhibit platelet function, resulting in impaired clot formation as well as impaired clot strength.



Fibrinolysis can be categorized as either physiological or pathophysiological. Physiological fibrinolysis begins with the initial generation of fibrin and occurs when plasmin binds to it, increasing the activity of plasmin against fibrin. In addition, fibrin-bound plasmin is protected from endogenous plasmin inhibitors, allowing the fibrinolytic reaction to occur unimpeded.

Pathophysiological fibrinolysis is associated with the presence of excess plasma-free plasmin. This excess plasmin overwhelms the endogenous anti-plasmin mechanisms, resulting in the consumption of fibrin, fibrinogen, and other coagulation factors and platelets. This consumption of coagulation factors may ultimately result in coagulation factor deficiencies.

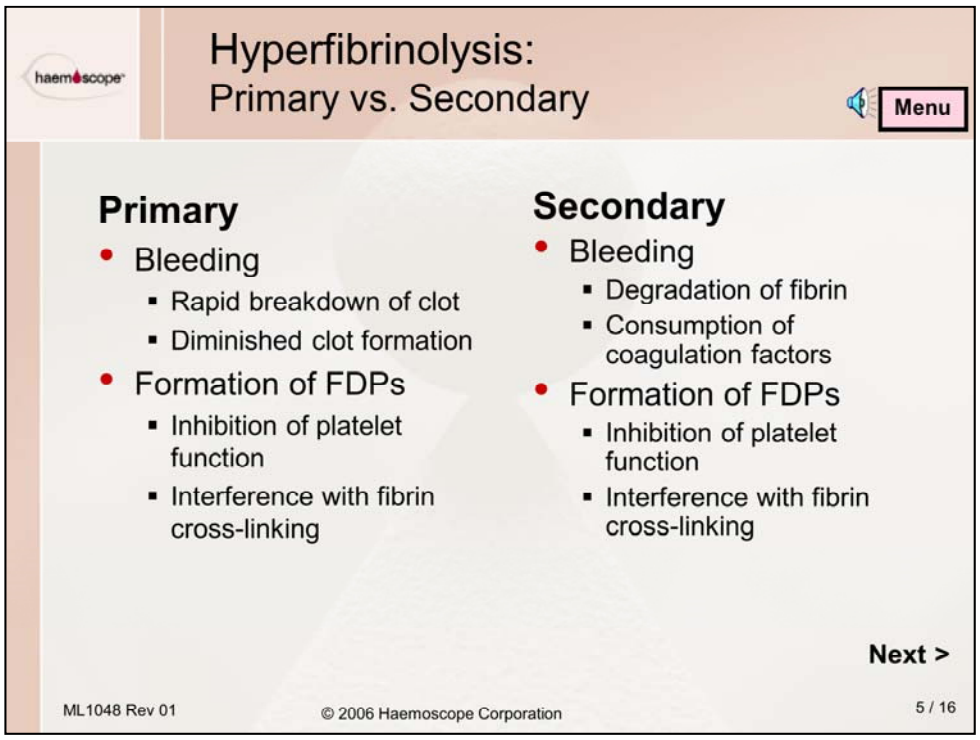
The degradation of fibrin and fibrinogen also leads to the generation of fibrin degradation products, or FDPs. These interfere with fibrin cross-linking and platelet function, resulting in impaired clot formation and possible bleeding.



Fibrinolysis that results in bleeding (i.e. hyperfibrinolysis) is further classified as primary or secondary. Primary fibrinolysis is associated with the rapid breakdown of clots resulting from an increase in circulating tissue plasminogen activator (tPA), a factor continually released into the plasma by endothelial cells. Free tPA has low plasminogen activating capability, but when bound to fibrin, its activity is significantly increased; therefore, under normal conditions, fibrinolysis is not initiated until fibrin is generated.

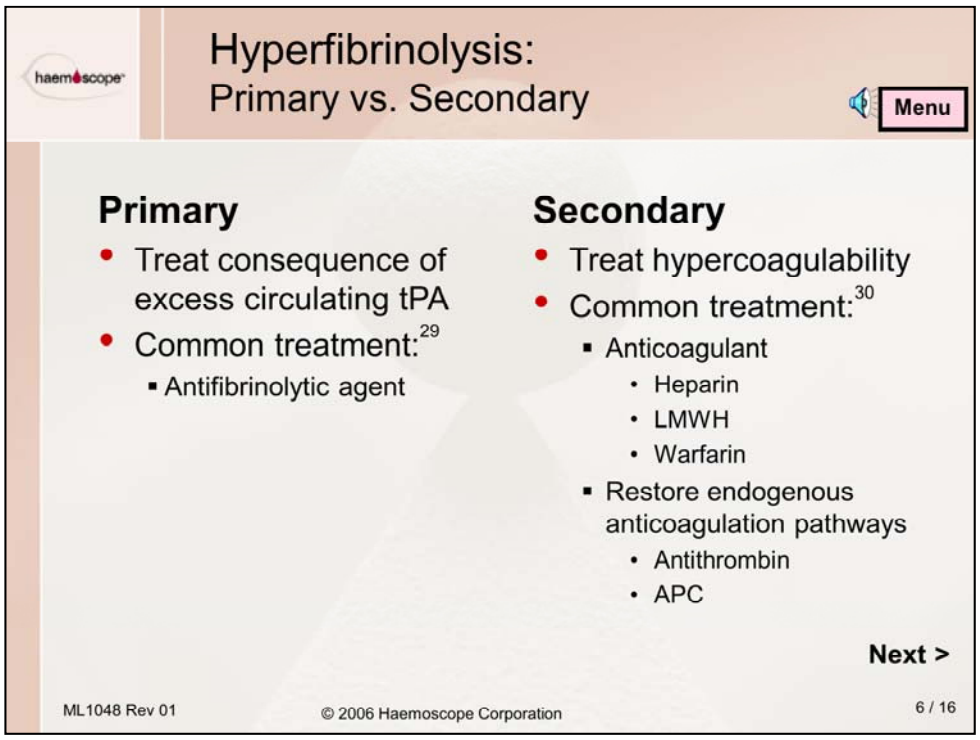
Primary fibrinolysis is pathophysiological in nature. In the presence of excess tPA, there may be sufficient activity to increase plasmin generation without the presence of fibrin, as well as to significantly increase plasmin levels after fibrin is generated. Both conditions contribute to an acceleration of fibrinolysis. The amount of circulating tPA may be increased by excess synthesis and release from the vascular endothelium, caused by excess activation, or by decreased hepatic clearance caused by liver dysfunction. Circulating tPA activity may also increase due to loss of endogenous plasmin or plasminogen inhibitors, such as α_2-antiplasmin or plasminogen activator inhibitor (PAI-1), also synthesized and released by the vascular endothelium.

Secondary fibrinolysis is secondary to a systemic hypercoagulable state and is in response to the generation of fibrin; it is a protective, or physiological response. The hypercoagulable state associated with this condition is systemic or microvascular in nature rather than localized. It is associated with a systemic inflammatory response, such as sepsis or DIC. Secondary fibrinolysis will persist as long as the hypercoagulable state continues.



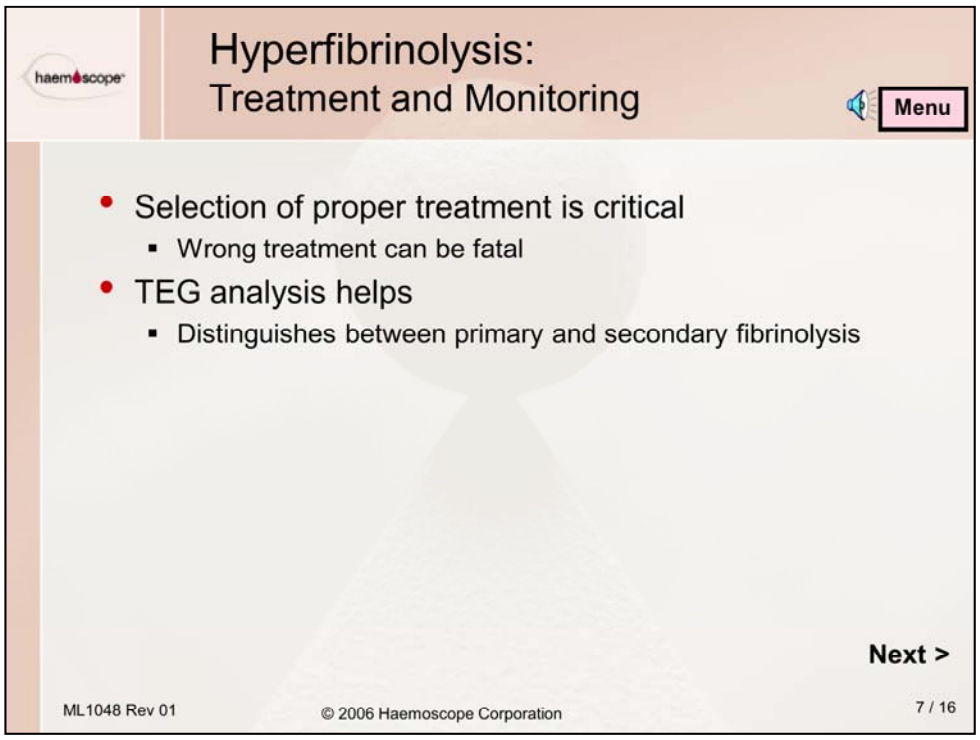
Both primary and secondary fibrinolysis can cause bleeding. In primary fibrinolysis, this is associated with reduction in clot strength due to rapid breakdown of clots and diminished clot formation, both due to the formation of FDPs caused by fibrin and fibrinogen degradation. FDPs inhibit platelet function and interfere with fibrin cross-linking.

In secondary fibrinolysis, bleeding is associated with degradation of fibrinogen and other coagulation factors. These coagulation factors are consumed, leading to an inability to generate thrombin. Also, as in primary fibrinolysis, FDPs are formed, resulting in impaired clot formation.



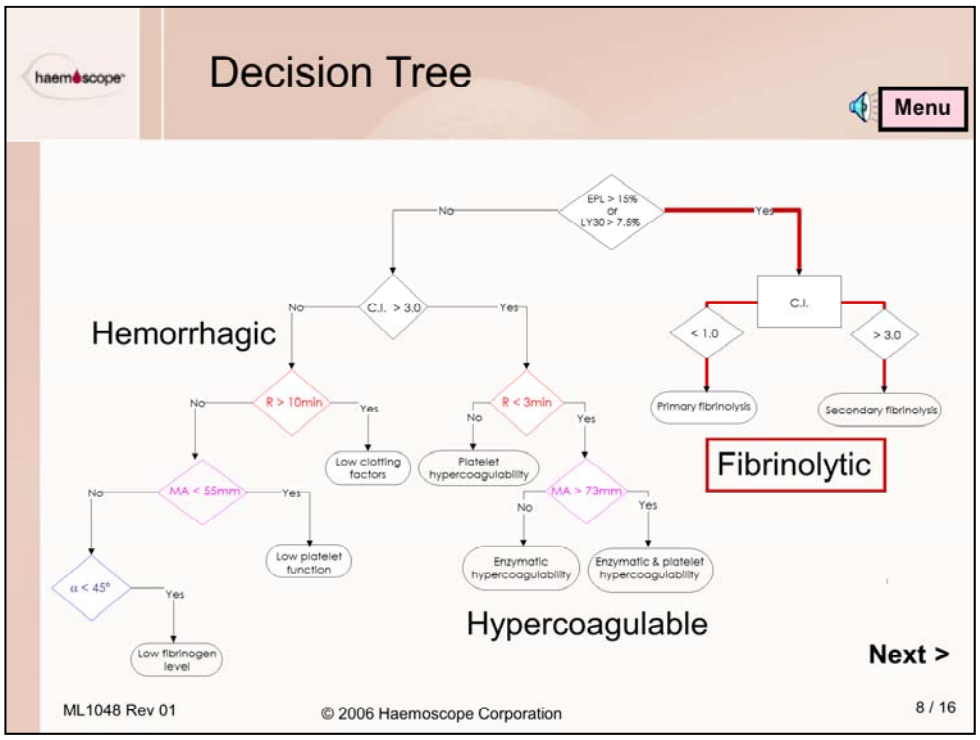
Since the causes of primary and secondary fibrinolysis are different, the treatments are also different. In the case of primary fibrinolysis, the goal is to treat excessive plasmin activity, which is the consequence of excess circulating tPA. Administration of an antifibrinolytic agent, with specific or non-specific anti-plasmin activity, is commonly the treatment of choice.[29]

However, in secondary fibrinolysis, the underlying cause is hypercoagulability. Thus, administration of an anticoagulant is appropriate. Common treatments may include agents that restore the endogenous anti-thrombotic or anticoagulant pathways, such as antithrombin, and activated protein C, heparin, low molecular weight heparin, and warfarin. [30]

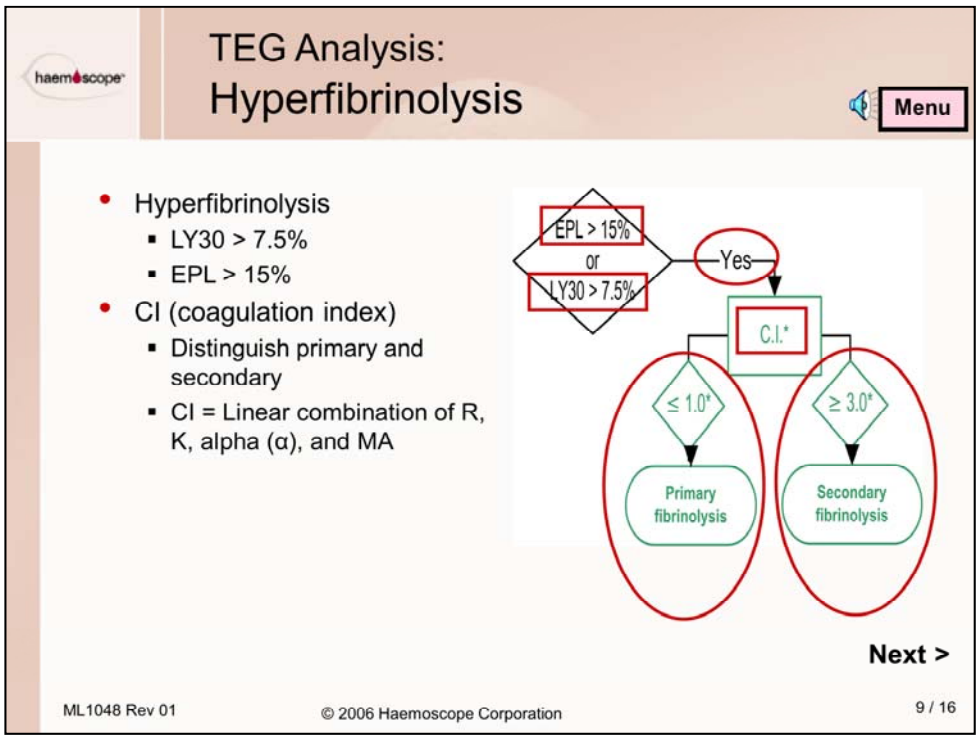


The selection of the proper treatment for fibrinolysis is critical to patient outcome. The wrong treatment can be fatal, in the case of secondary fibrinolysis.

Administration of an antifibrinolytic agent to a patient with secondary fibrinolysis will inhibit the protective effects of fibrinolysis, resulting in systemic thrombotic activity. Consequently, the ability to differentiate between primary and secondary fibrinolysis is crucial. TEG analysis can help distinguish between these two conditions.

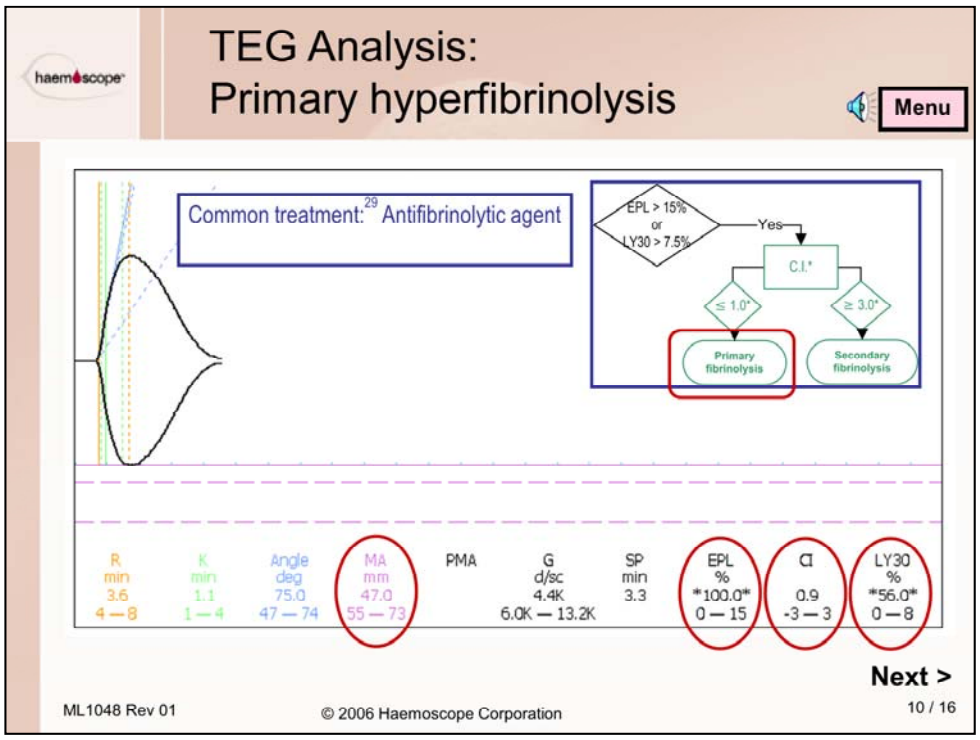


The quantitative TEG decision tree is useful in identifying fibrinolysis, and in differentiating between primary and secondary fibrinolysis.



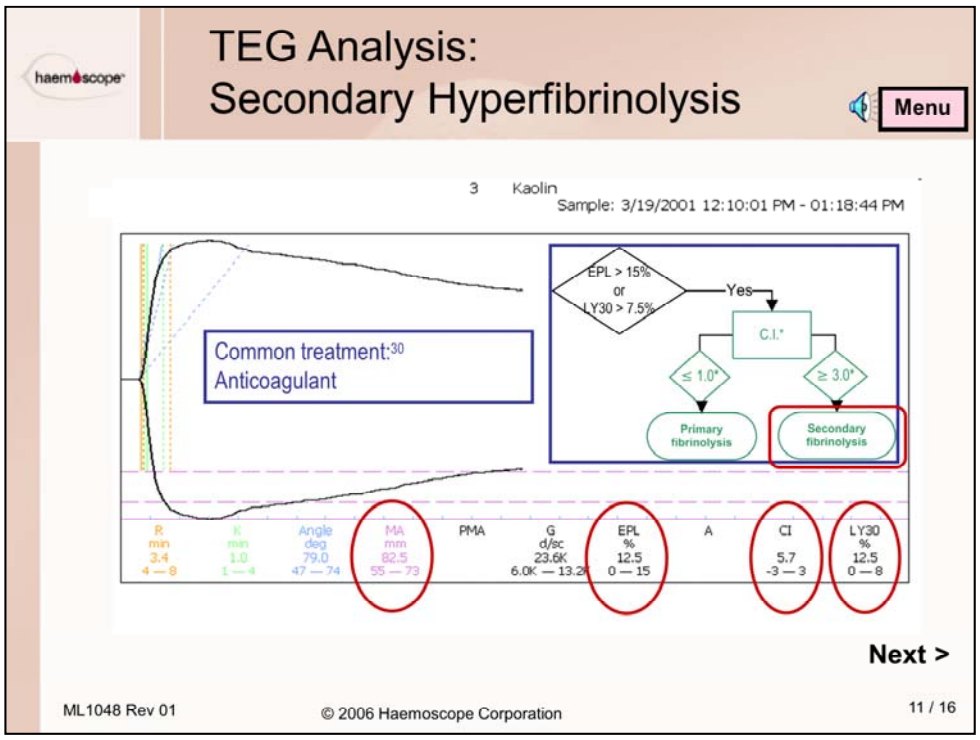
The TEG decision tree identifies hyperfibrinolysis by an LY30 value (lysis at 30 minutes after MA) greater than 7.5% or an EPL value (estimated percent lysis) greater than 15%. Both parameters monitor the reduction of clot strength over time.

The CI (coagulation index) is used to distinguish between primary and secondary fibrinolysis. A CI value less than or equal to 1.0 suggests primary fibrinolysis, and a CI value greater than 3.0 suggests secondary fibrinolysis.



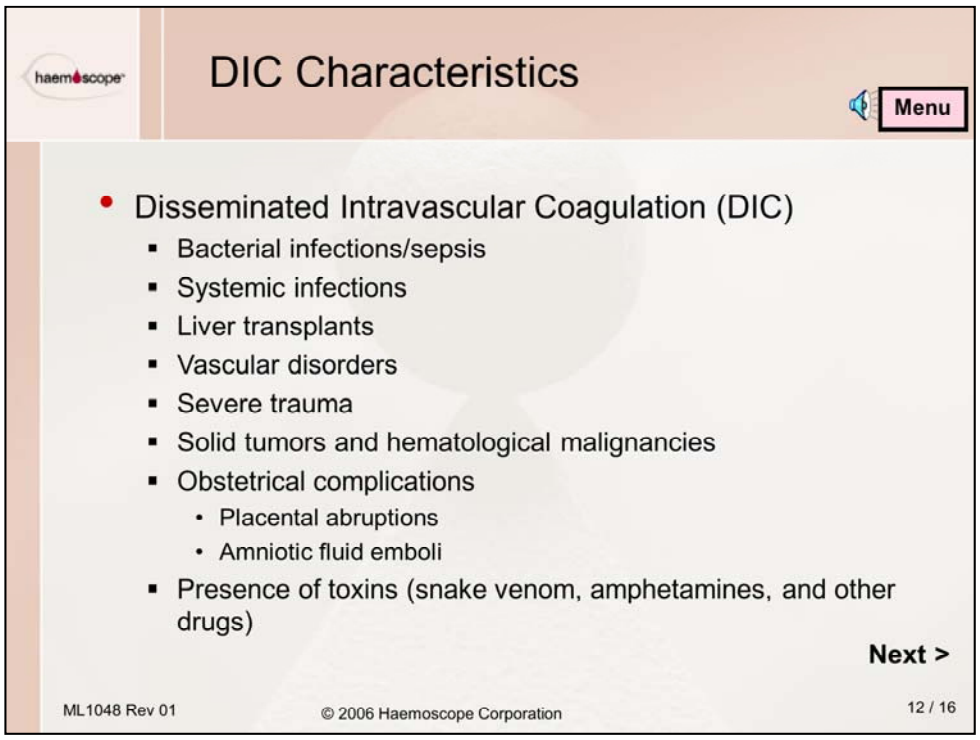
This tracing is an example of primary fibrinolysis. Both the LY30 and EPL values are greater than normal, and the CI value of 0.9 is less than 1.0. The MA value is also low.

In this case, the common treatment would be an antifibrinolytic agent.[29]



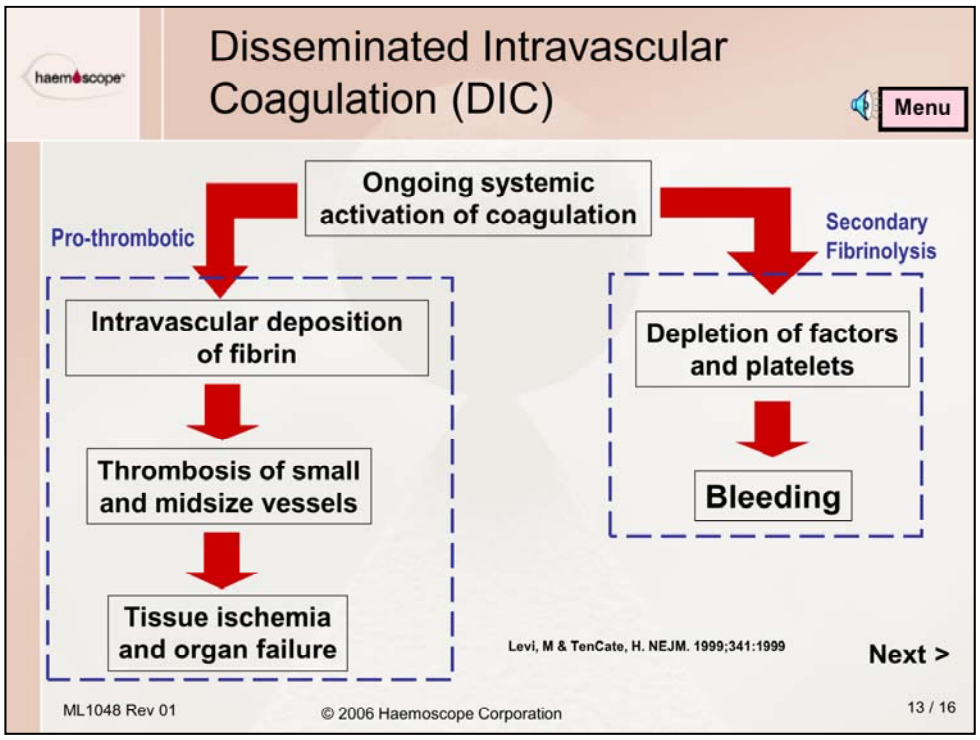
This tracing shows secondary fibrinolysis. Again, the LY30 and EPL values are greater than normal. But in this case, the CI value is greater than 3.0, suggesting a hypercoagulable state. The MA value is also high.

The common treatment would be administration of an anticoagulant agent.[30]



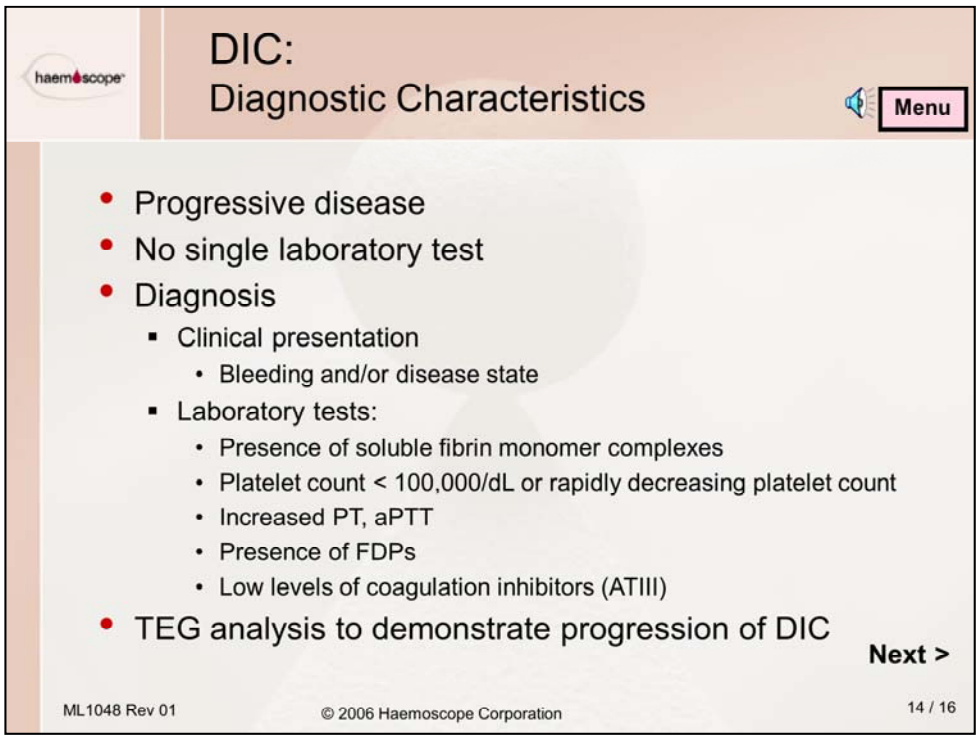
Disseminated intravascular coagulation (DIC) is a common acquired disorder associated with a variety of clinical conditions, most of which have a systemic inflammatory component. These conditions include:

- Bacterial infections and sepsis
- Other systemic infections
- Liver transplants
- Vascular disorders
- Severe trauma
- Solid tumors and hematological malignancies
- Obstetrical complications such as placental disruptions and amniotic fluid emboli
- The presence of toxins such as snake venom and some types of drugs



DIC is characterized by ongoing systemic activation of coagulation. This has dual consequences in the progression of the disease. On the one hand, it leads to intravascular deposition of fibrin, with subsequent formation of thrombi in small and midsized blood vessels, which in turn leads to tissue ischemia and eventual organ failure.

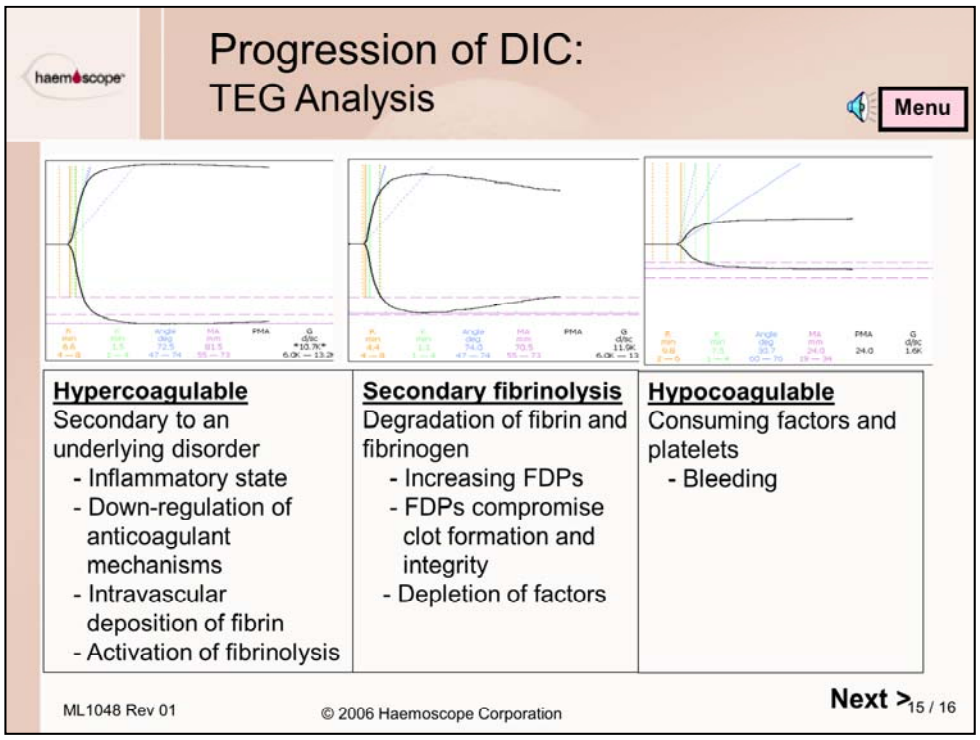
On the other hand, it also activates fibrinolysis. The resulting cycle of clot formation and breakdown eventually depletes coagulation factors and platelets, leading to the complete disruption of hemostatic balance, and ultimately to bleeding (Levi, 1999).



DIC is a progressive disease, starting with a hypercoagulable state and progressing to hypocoagulable. Monitoring of the hemostatic aspect is challenging, and diagnosis requires information regarding the patient's clinical presentation and history, as well as a series of laboratory test results — there is no single test that can conclusively establish or rule out DIC.

The clinical presentation of a patient with DIC is either bleeding or a disease state known to be associated with DIC. Laboratory tests are used to support or refute the diagnosis. Important tests include the presence of soluble fibrin monomer complexes, platelet counts of less than 100,000/dL or a rapidly decreasing platelet count, increased PT and aPTT values, the presence of FDPs, and low levels of endogenous anticoagulation or antithrombotic agents such as antithrombin.

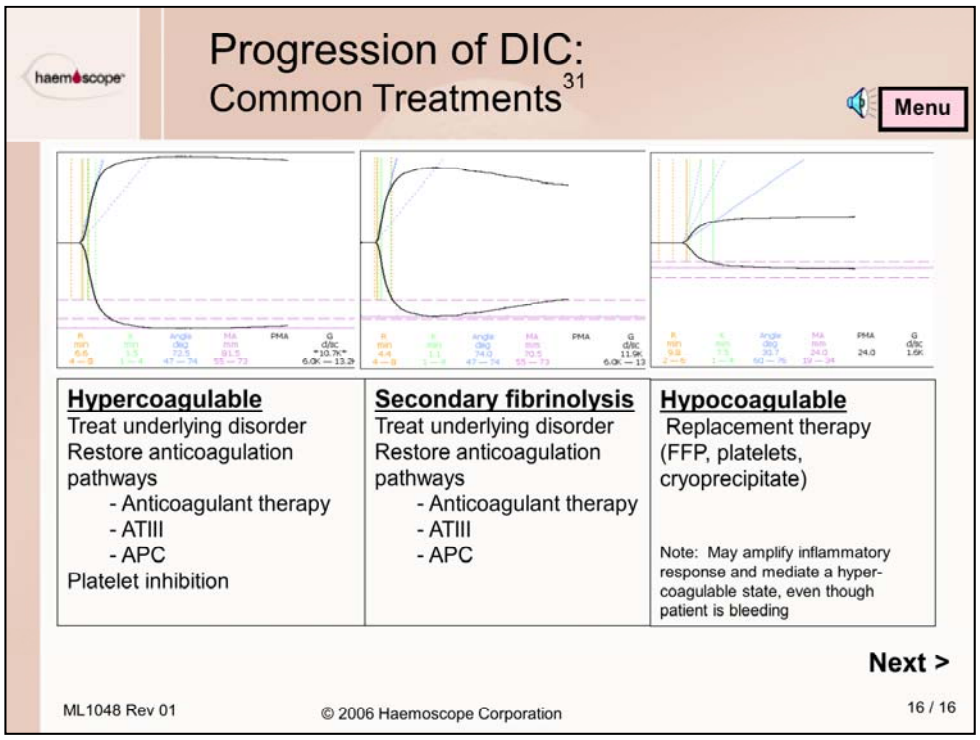
TEG analysis can also be useful in identification of DIC. In addition, it is able to demonstrate the progression of the disease over time.



These three TEG tracings demonstrate the progression of DIC. The first shows hypercoagulability — platelet, enzymatic, or a combination of both. This is secondary to an underlying disorder, such as a systemic inflammatory state or down-regulation of endogenous anticoagulant mechanisms. It is also associated with the intravascular deposition of fibrin, especially microvascular, which activates fibrinolysis, causing DIC to progress to the second phase, secondary fibrinolysis.

During the second phase, fibrinolysis causes the degradation of fibrin and fibrinogen, increasing the level of FDPs. These excess FDPs in turn compromise clot formation, integrity, and strength. Fibrinolysis also degrades other coagulation factors, leading to their depletion and to an inability to generate thrombin.

Finally, the cycle of clot formation and breakdown consumes factors and platelets, eventually leading to a total inability to clot. Thus, the third stage of DIC is characterized by hypocoagulability and bleeding.

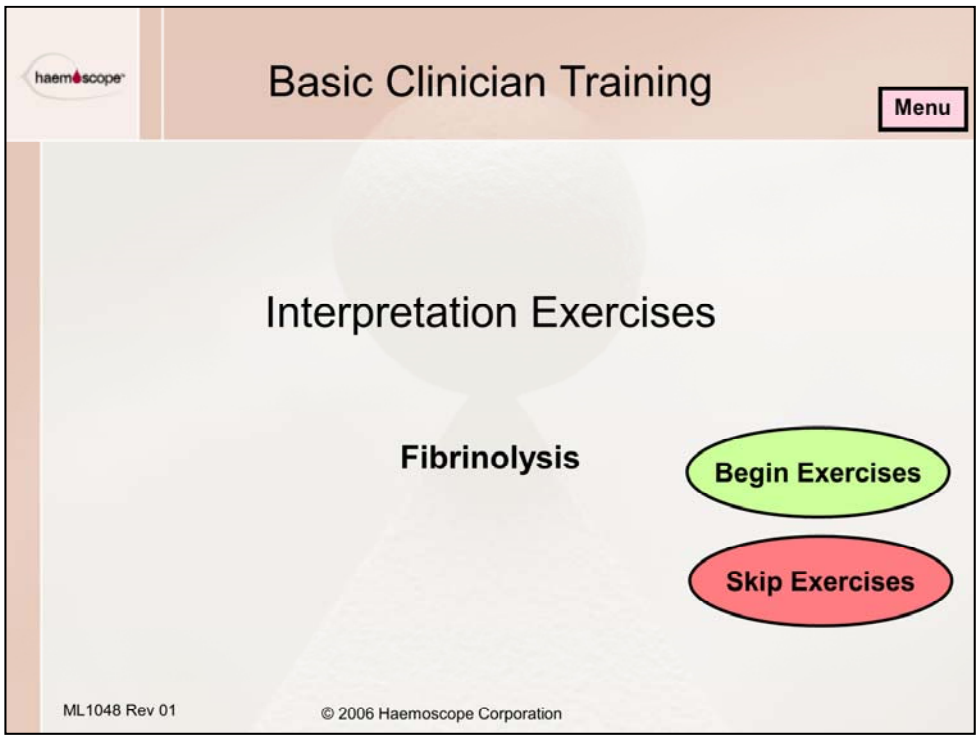


Since DIC is a progressive disease, the earlier a patient is treated, the better the chance of a positive outcome. Treatment during the hypercoagulable phase centers around the underlying disorder, usually inflammatory in nature. It may also involve restoration of endogenous anticoagulation pathways disrupted by the inflammatory response. These treatments commonly include anticoagulant therapy, antithrombin therapy, or administration of activated protein C (APC). In addition, a platelet inhibitor may disrupt the coagulation response, decreasing fibrin formation and preserving platelets and coagulation factors.[31]

In Phase Two, treatment still revolves around the underlying disorder. Since fibrinolysis is activated, emphasis is on inhibiting clot formation through use of an anticoagulant or agents that increase the endogenous anticoagulant mechanisms.

Once DIC has progressed to the hypocoagulable phase, it is difficult to reverse the process because of the magnitude of the imbalance in the hemostatic and inflammatory systems. The common treatment in this phase is to attempt to replace hemostatic components (i.e platelets, FFP, cryoprecipitate).

By Phase Three, bleeding is due to factor and platelet deficiencies, but the underlying cause of the initial hypercoagulable response may still be present. Thus, replacement of blood components may exacerbate the inflammatory response, mediating a hypercoagulable state even though the patient is bleeding.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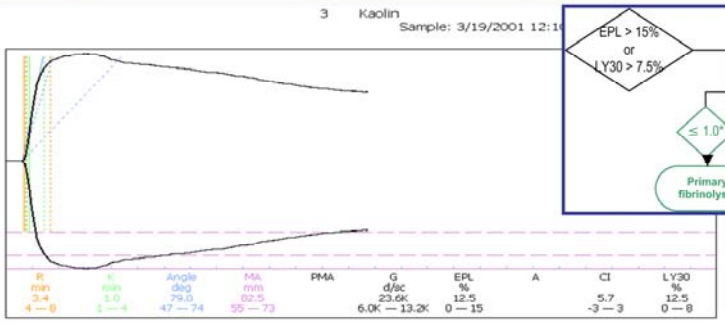
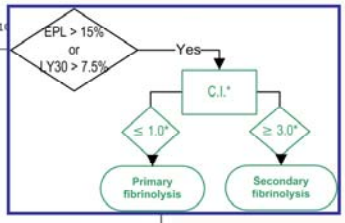
Exercise 1





Using the TEG decision tree, what is a likely cause(s) of bleeding in this patient? (Select all that apply)

a) Residual anticoagulant
b) Surgical bleeding
c) Primary fibrinolysis
d) Secondary fibrinolysis

What treatment(s) would you consider for this patient?

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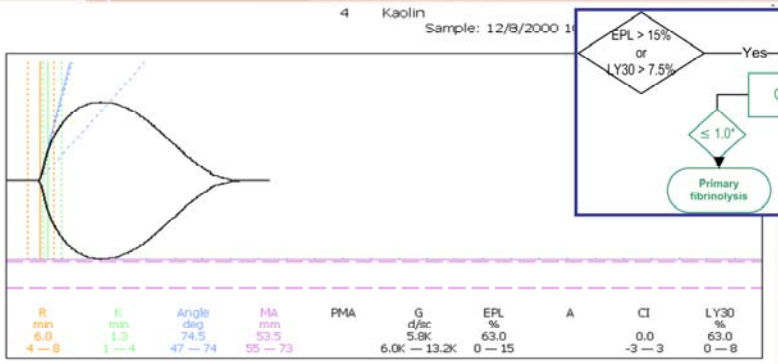
Exercise 2



Using the TEG decision tree, what is a likely cause(s) of bleeding in this patient? (Select all that apply)

a) Residual anticoagulant
b) Surgical bleeding
c) Primary fibrinolysis
d) Secondary fibrinolysis

What treatment(s) would you consider for this patient?

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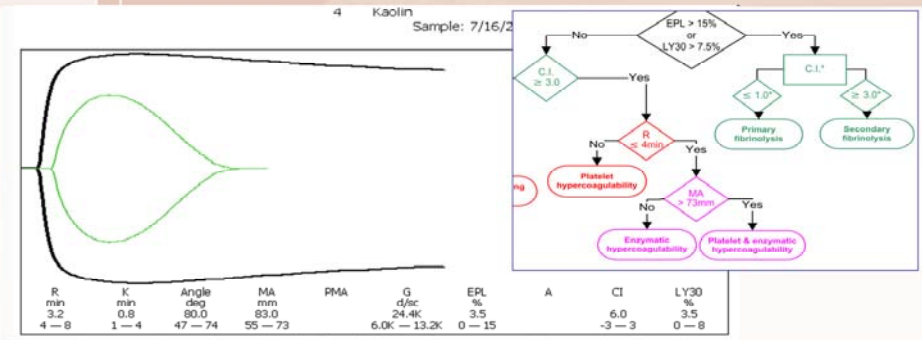
Exercise 3



This patient was brought to the OR for CABGx4, on pump. Due to the initial hyper-coagulable state (black tracing), no prophylactic antifibrinolytic was administered. The rewarming TEG (green tracing) indicated development of primary fibrinolysis.
What would be a common treatment plan for this patient?

a) Consider administering an antifibrinolytic agent before termination of CPB. Repeat TEG.
b) Consider administering an antifibrinolytic agent after CPB and protamine administration. Repeat TEG.
c) Consider no treatment. Repeat TEG post-protamine.
d) Consider administering an antifibrinolytic agent during CPB and platelets post-protamine.

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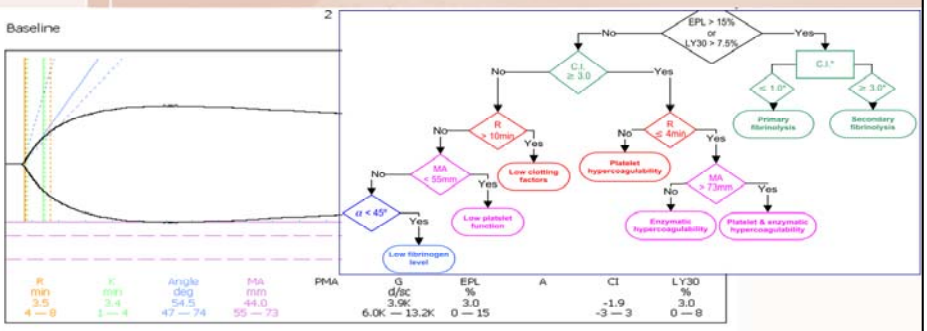
Exercise 4



This patient was brought to the OR for CABGx4, on pump. While opening the chest, the surgeon commented that the patient was 'oozy.' What is the mostly likely cause of this condition?

a) Fibrinogen deficiency
b) Platelet deficiency/defect
c) Fibrinolysis
d) Hemodilution

Would treatment with an antifibrinolytic agent be contra-indicated? Yes or No.
If no, which antifibrinolytic agent would you use?

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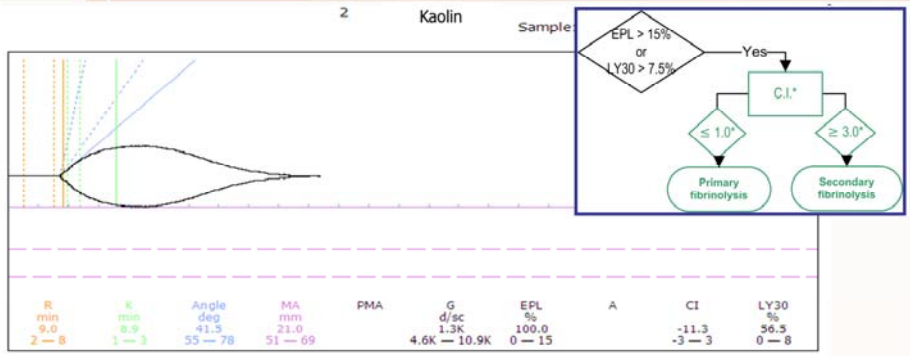
Exercise 5



Using the TEG decision tree, what is a likely cause(s) of bleeding in this patient? (Select all that apply)

a) Residual anticoagulant
b) Surgical bleeding
c) Primary fibrinolysis
d) Secondary fibrinolysis

What treatment(s) would you consider for this patient?

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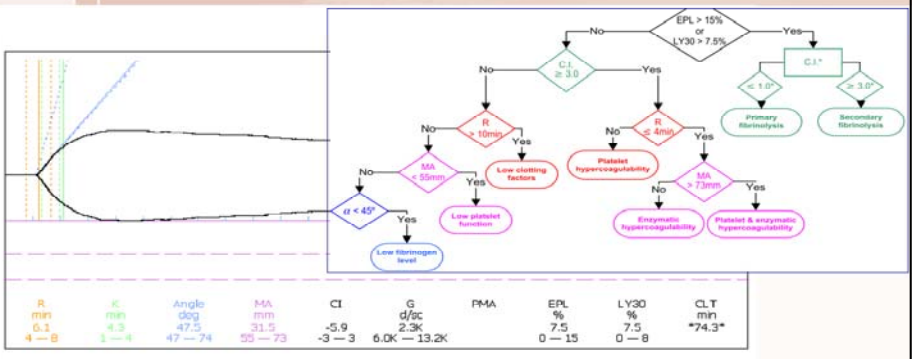
Exercise 6



Using the TEG decision tree, what is a likely cause of bleeding in this patient? (Select all that apply)

a) Factor deficiency
b) Platelet deficiency/dysfunction
c) Primary fibrinolysis
d) Secondary fibrinolysis

What treatment(s) would you consider for this patient?

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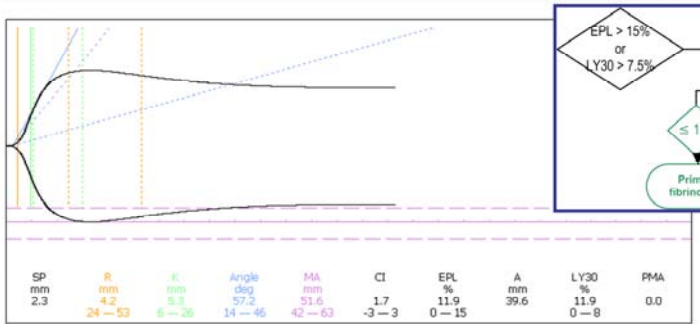
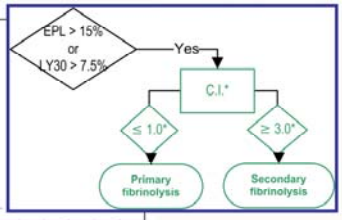
Exercise 7





Using the TEG decision tree, what is your interpretation of this tracing?
(Select all that apply)

a) Primary fibrinolysis
b) Secondary fibrinolysis
c) Fibrinolysis
d) Surgical bleeding
e) Platelet adhesion defect

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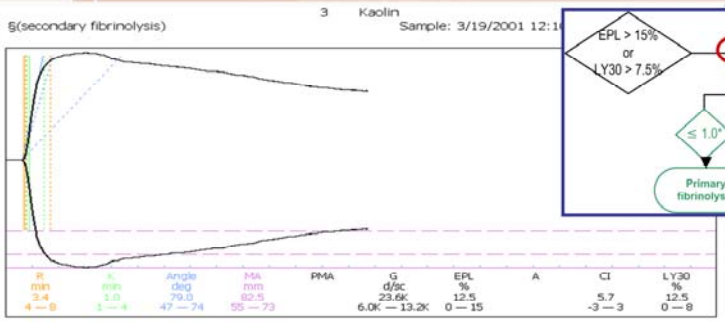
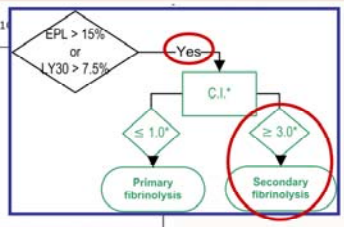
Answer to Exercise 1





Using the TEG decision tree, what is a likely cause(s) of bleeding in this patient? (Select all that apply)

a) Residual anticoagulant
b) Surgical bleeding
c) Primary fibrinolysis
d) Secondary fibrinolysis

What treatment(s) would you consider for this patient? Consider treating the underlying disorder, plus an antiplatelet agent and an anticoagulant to inhibit or reduce thrombin generation.[31, 30]

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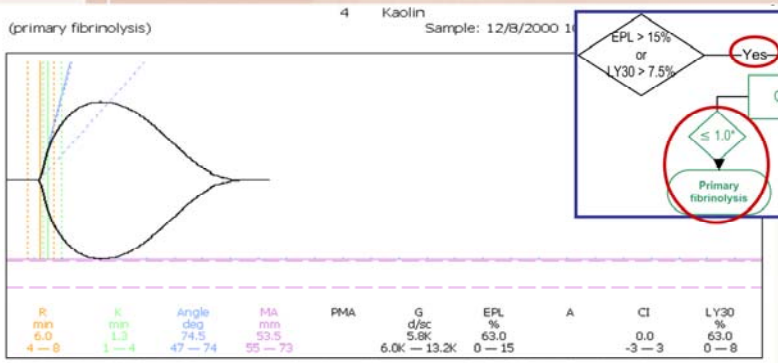
Answer to Exercise 2



Using the TEG decision tree, what is a likely cause(s) of bleeding in this patient? (Select all that apply)

a) Residual anticoagulant
b) Surgical bleeding
c) Primary fibrinolysis
d) Secondary fibrinolysis

What treatment(s) would you consider for this patient?

Antifibrinolytic agent[28]

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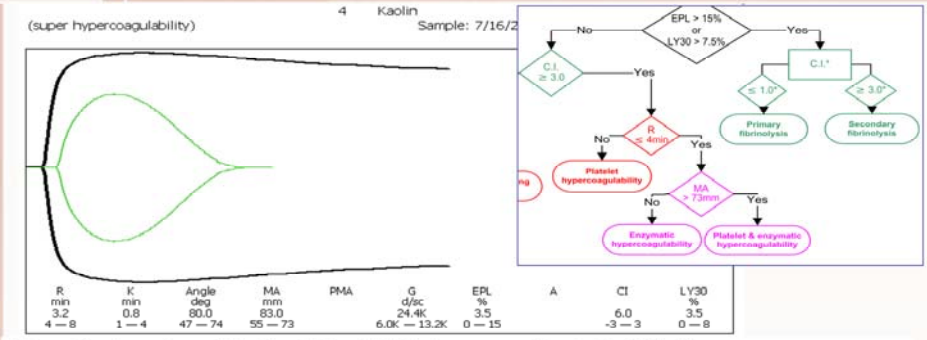
Answer to Exercise 3



This patient was brought to the OR for CABGx4, on pump. Due to the initial hyper-coagulable state (black tracing), no prophylactic antifibrinolytic was administered. The rewarming TEG (green tracing) indicated development of primary fibrinolysis.
What would be a common treatment plan for this patient?

a) Consider administering an antifibrinolytic agent before termination of CPB. Repeat TEG. Since fibrinolysis on pump can be transient, repeat TEG. If fibrinolysis persists, treat with antifibrinolytic agent and monitor the effect.[29]

b) Consider administering an antifibrinolytic agent after CPB and protamine administration. Repeat TEG.

c) Consider no treatment. Repeat TEG post-protamine.

d) Consider administering an antifibrinolytic agent during CPB and platelets post-protamine.

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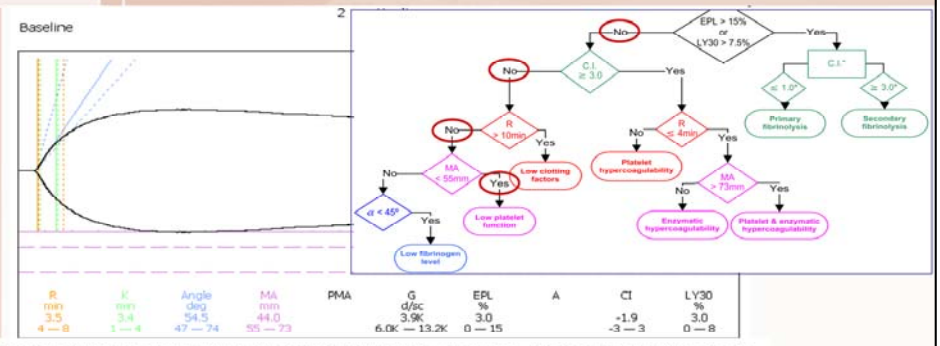
Answer to Exercise 4



This patient was brought to the OR for CABGx4, on pump. While opening the chest, the surgeon commented that the patient was 'oozy.' What is the mostly likely cause of this condition?

a) Fibrinogen deficiency

b) Platelet deficiency/defect

c) Fibrinolysis

d) Hemodilution

Would treatment with an antifibrinolytic agent be contra-indicated? No

If no, which antifibrinolytic agent would you use?

Consider aprotinin for potential platelet-protecting effects.[29]

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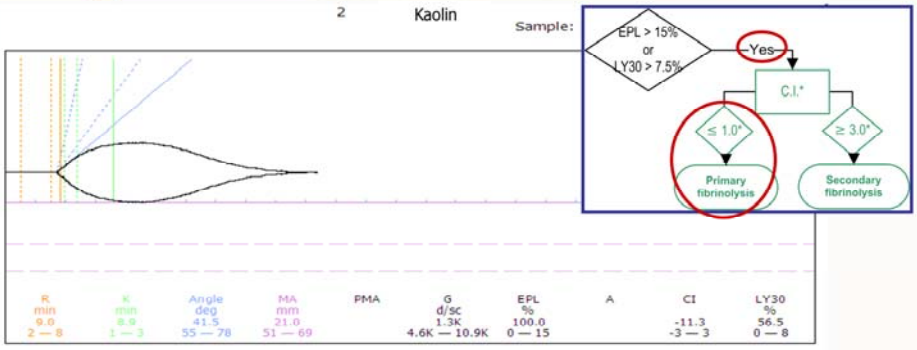
Answer to Exercise 5



Using the TEG decision tree, what is a likely cause(s) of bleeding in this patient? (Select all that apply)

a) Residual anticoagulant
b) Surgical bleeding
c) Primary fibrinolysis
d) Secondary fibrinolysis

What treatment(s) would you consider for this patient? Consider treating with antifibrinolytic agent first. If patient continues to bleed, repeat TEG to determine need for platelets or factors.[29]

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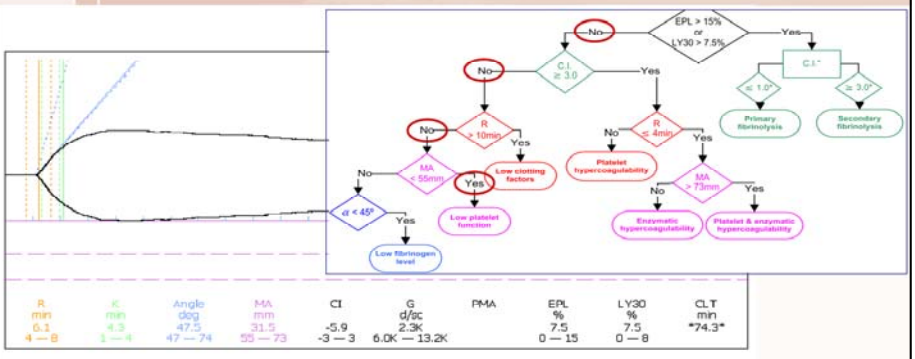
Answer to Exercise 6



Using the TEG decision tree, what is a likely cause of bleeding in this patient? (Select all that apply)

a) Factor deficiency

b) Platelet deficiency/dysfunction

c) Primary fibrinolysis

d) Secondary fibrinolysis

What treatment(s) would you consider for this patient?

Consider treating with platelet transfusion. If patient continues to bleed, repeat the TEG to determine possible contribution of fibrinolysis.[29]

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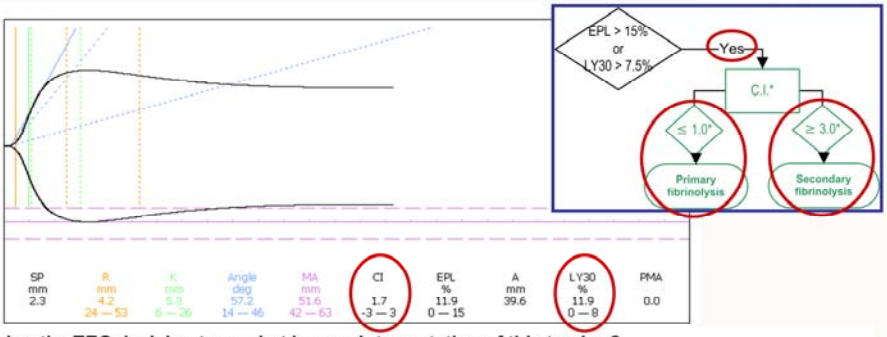
Answer to Exercise 7



Using the TEG decision tree, what is your interpretation of this tracing?
(Select all that apply)

a) Primary fibrinolysis (cannot rule out)
b) Secondary fibrinolysis (cannot rule out)
c) Fibrinolysis
d) Surgical bleeding
e) Platelet adhesion defect

Although fibrinolysis is present, the CI value is outside those given for designation as primary or secondary. Knowledge of patient history, drug history, other laboratory tests, and bleeding status would be required to make a definitive diagnosis. A clinical presentation of DIC would suggest secondary fibrinolysis, and treatment with an anticoagulant.[29]

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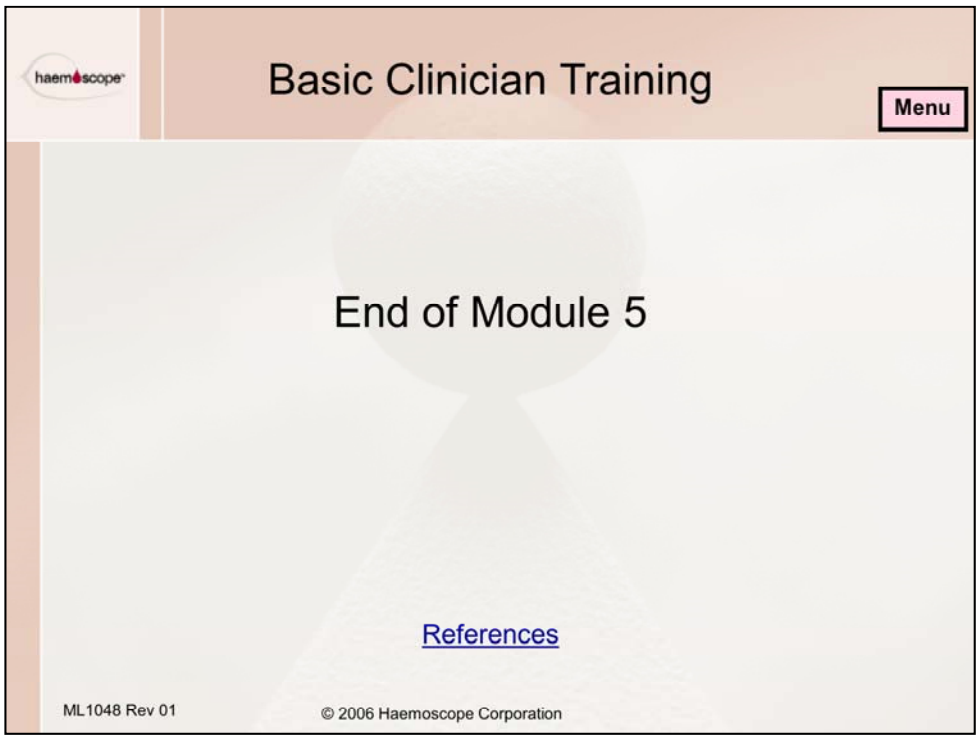
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